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# Nonmotor Disturbances in Parkinson's Disease

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**Key Words**
Parkinson's disease · Nonmotor disturbances · Depression · Anxiety · Fatigue · Diagnosis · Quality of life

**Abstract**
Nonmotor disturbances (NMDs) affect most patients with Parkinson's disease (PD) and often have a profound impact on their quality of life. NMDs such as depression, anxiety, fatigue, REM sleep behavior disorder, constipation, delayed gastric emptying, altered olfaction and pain can precede the onset of motor symptoms. Other NMDs, including hallucinations, dementia, excessive daytime sleepiness, insomnia, orthostatic hypotension and bladder disturbances, typically appear later in the course of PD. For most NMDs of PD, nondopaminergic and non-nigrostriatal mechanisms (e.g. neurodegeneration of other transmitter systems in the cortex and brainstem, side effects of medications, genetic and psychosocial factors) are considered more relevant than the 'classical' dopaminergic-nigrostriatal dysfunction. The recognition of NMDs requires a high degree of clinical suspicion, the use of specific questionnaires and ancillary tests. Pharmacological and nonpharmacological approaches can be effective, but for most forms of treatment of NMDs, the scientific evidence is limited. 

## Introduction

Only recently have the frequency and relevance of nonmotor disturbances (NMDs) of Parkinson's disease (PD) been recognized. Accordingly, a questionnaire addressing nonmotor symptoms in PD was recently developed and used in an international multicenter pilot study [1]. Also, the new, revised Unified Parkinson's Disease Rating Scale takes NMDs into account more thoroughly [2]. Finally, in 2010, the American Academy of Neurology issued a practice parameter paper about treatment of NMDs. Only sildenafil citrate (for erectile dysfunction), macrogol (polyethylene glycol for constipation) and levodopa/carbidopa (for spontaneous nighttime leg movements) were considered to be sufficiently proven to be effective in PD (evidence level B or C) [3].

Some NMDs have a diagnostic value because they appear early in the course of PD and may precede the onset of motor symptoms. Other NMDs typically appear later and have a profound impact on the quality of life of PD patients.

Based not only on clinical but also neuropathological data, PD, which was traditionally seen as a dopaminergic motor disorder, can now be viewed as a multisystem neurodegenerative disease that often involves other neu-

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rotransmitter systems and affects nonmotor functions. This paper reviews the clinical features, underlying mechanisms, diagnosis and treatment of neuropsychiatric/cognitive, sleep-wake, autonomic and sensory disturbances in PD.

## Neuropsychiatric/Cognitive Disturbances

### *Depression*

Clinical Features

Depression is found in 25–50% of PD patients and can appear early in the course of PD [4]. Suicidal ideations may be present in up to 10% of patients. Conversely, severe depression and suicide attempts are rather uncommon. They have been reported following subthalamic stimulation [5].

Depression is associated with apathy, anxiety, excessive daytime sleepiness (EDS), cognitive decline and poor quality of life [6, 7]. In addition, dysphoria and depression predispose to impulse control disorders (ICDs) in PD.

Mechanisms

Impaired dopaminergic and probably later in the course of PD also serotonergic and noradrenergic transmission in the ventral striatum and limbic system has been suggested as a possible mechanism [4, 8]. A familial predisposition has also been observed [4].

Abrupt cessation of dopaminergic drugs can lead to depression/suicidal thoughts. Depression can also appear acutely as a nonmotor fluctuation manifestation or following high-frequency deep brain stimulation [9].

Psychoreactive mechanisms may also be involved in PD-associated depression.

Diagnosis

Apathy, fatigue, sleepiness and slow motion can be difficult to differentiate from (and do actually commonly coexist with) depression. The Beck Depression Inventory and the Hamilton Depression Rating Scale have been used to assess depression in PD, although some physical symptoms of depression might overlap with those of PD [10].

Treatment

Pramipexole, ropinirole and other dopaminergic agents/drugs may improve depression, particularly in the early course of PD [4, 11]. Antidepressants (amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (SSRIs; e.g. venlafaxine) and noradrenaline reuptake inhibitors (e.g. reboxetine) have been shown in a few studies to improve mood in PD [4, 12]. However, their potential side effects [including orthostatic hypotension (OH) and cognitive side effects] should be considered. Mirtazapine is better tolerated in advanced PD [pers. observation].

In patients with PD, depression and hypersomnia/EDS/fatigue, reboxetine and venlafaxine are preferable. Conversely, in PD patients with insomnia, mirtazapine could be tried first.

### *Anxiety and Panic Attacks*

Clinical Features

Panic attacks, phobias and anxiety are seen in about 40% of PD patients [4]. They can appear early in the course of PD but may also be seen in the context of nonmotor fluctuations ('off states') of more advanced PD.

Anxiety is associated with depression and insomnia.

Mechanisms

The role of dopamine and other neurotransmitters remains speculative. Anxiety and panic attacks, often in association with other psychiatric and somatic symptoms (such as depression, dysphoria, sweating, pain and OH), can be observed in the course of withdrawal from dopaminergic drugs, in particular agonists (the so-called dopamine agonist withdrawal syndrome) [13].

Diagnosis

The Hospital Anxiety and Depression Scale and other anxiety scales have been suggested, but their validity has not been well assessed [4].

Treatment

There are only poor data about the treatment of anxiety in PD. Dopaminergic drugs, SSRIs and benzodiazepines may be useful. However, the latter can worsen gait, cognition and sleep breathing. Deep brain stimulation may also lead to an improvement in anxiety [11].

### *Impulse Control Disorders*

Clinical Features

ICDs include a series of disturbances such as compulsive gambling and shopping; binge eating; hypersexuality; punding (abnormal, repetitive, meaningless activities, obsessive cleaning, arranging); compulsive medication use (so-called hedonistic homeostatic dysregulation or dopamine dysregulation syndrome); hobbyism (fig. 1), and excessive, aimless wandering or driving [14–16]. This

spectrum of disorders is associated with significant psychosocial distress and consequences.

The frequency of ICDs in PD is poorly known; it may range from 1 to 14% and largely depends on the diagnostic criteria used and the specific type of ICD considered [16, 17].

Young age of onset, male gender, higher doses of short-acting dopaminergic drugs (in particular dopamine agonists), psychiatric comorbidities, pre-existing drug or alcohol use and a novelty-seeking personality are linked with ICDs [18]. A recent large-scale study suggested that dopamine agonist treatment in PD is associated with 2- to 3.5-fold increased odds of having ICDs [19]. Cases of ICD induced (but also improved) by deep brain stimulation have also been reported.

Mechanisms

Overactivity of dopamine (basal ganglia) and underactivity of inhibitory (prefrontal) pathways have been suggested as mechanisms causing ICDs [15]. Neuroimaging studies have documented changes in the ventral striatum and prefrontal cortex [20]. The role of dopamine treatment is underscored by the observation that ICD is also present in patients with restless legs syndrome (RLS) [22].

Diagnosis

Patients rarely report ICDs, which often remain unrecognized. A recently developed, 30-question screening questionnaire was reported to have a >80% sensitivity (but a low specificity) for ICDs in PD [17].

Treatment

Reduction/cessation/change of dopaminergic drugs, use of new antipsychotic drugs, cognitive-behavioral treatments and psychological support/interventions can completely reverse ICDs in individual patients. However, the general prognosis of ICDs in PD is unclear [22].

***Hallucinations/Illusions/Psychosis***

Clinical Features

When systematically searched for, mild hallucinations and illusions (misperception of real stimuli) are found in up to 50% of patients with PD [23]. The onset of hallucinations within the first 3 years of PD suggests a diagnosis of dementia with Lewy bodies (DLB) [24].

Visual hallucinations/illusions are most commonly observed [25]. Typically, faces and persons (familiar or unfamiliar) and, less commonly, animals or objects are reported (fig. 2). Hallucinations in other modalities (including the tactile and olfactory domains) as well as multimodal hallucinations are possible [26]. Mild forms of hallucinations and illusions include the vague, fleeting vision of a passing animal/object ('passing illusions') and of the presence of a person ('sensed presence'). Capgras syndrome and other misidentification disturbances can also be observed. Insight may be preserved, particularly in cognitively intact patients. Hallucinations are more common during the wake-sleep transition and in the dark.

Hallucinations are associated with cognitive decline, depression, anxiety, sleep-wake disturbances and vivid dreaming [27]. Severe, frequent and chronic hallucinations (and psychosis) are a risk factor for nursing home placement and death.

Mechanisms

Mesopontine/limbic cholinergic underactivity and striatal dopaminergic overactivity have been discussed [28]. However, dopamine appears to be neither sufficient nor necessary for the occurrence of hallucinations in PD (for this reason, the use of the term 'dopamine psychosis' is not recommended). Abnormal activation of the higher-order visual (visuoperceptual) cortex, but also dysfunction of amygdaloid and retinal circuits have also been discussed [29]. Damage to the left hemisphere (right-predominant motor symptoms) has been linked with PD-related psychosis [30].

Diagnosis

Patients are reluctant to report hallucinations. However, the recognition of mild hallucinations is important to prevent PD-related psychosis. Tools for the recognition of PD-associated psychosis have been developed but not yet validated [31].

Treatment

Reduction of dopaminergic drugs is often but not always effective/sufficient in improving hallucinations/illusions. Reduction of anxiety and sleepiness may have a positive effect. Hospitalization may reduce (but occasionally also worsen) hallucinations. Improvement of coping strategies should be considered. Low-dose clozapine (typically, 6.25–50 mg are sufficient) improves hallucinations without worsening motor functions [32, 33] and appears to be superior to quetiapine [4]. Cholinesterase inhibitors may also be effective in reducing hallucinations and delusions by simultaneously exerting beneficial effects on cognition.

**Fig. 1.** A 60-year-old architect with mild PD and dopamine dysregulation syndrome (hedonistic homeostatic syndrome) who used to make drawings and sketches in the past started in the course of his neurological disorder to produce large, complex and colorful paintings. He reports that these paintings are done 'as if in a trance', without preparation and 'just like that' in a few minutes.

**Fig. 2.** A 70-year-old woman with mild PD had visual hallucinations (the face of her father) that she always perceived when staring at the chair of her living room. On the right, the visual misperception of the patient is reconstructed (with a projection of a picture of her father) [Brugger A., Bassetti C., unpubl. observations].

### *Dementia*

Clinical Features

Dementia is present in up to 80% of PD patients towards the end of their life [34, 35]. The onset of dementia within the first year of PD ('1-year rule') suggests a diagnosis of DLB [24].

Clinically, patients present with dysexecutive syndrome (short attention span, poor working memory, difficulty in planning/set-shifting/multitasking, reduced drive/psychomotor slowing, decreased verbal fluency, perseverations) and visuospatial deficits. Cognition and attention typically fluctuate; patients exhibit daytime drowsiness and lethargy, daytime sleep of 2 or more hours, episodes of staring into space for long periods and episodes of disorganized speech [36]. Memory and language deficits are observed only later in the course of PD dementia (PDD), where memory retrieval in the free recall mode is typically more compromised than cued recall.

Hallucinations, depression, EDS, sleep disturbances and urinary incontinence are frequently found in patients with PDD [35, 37].

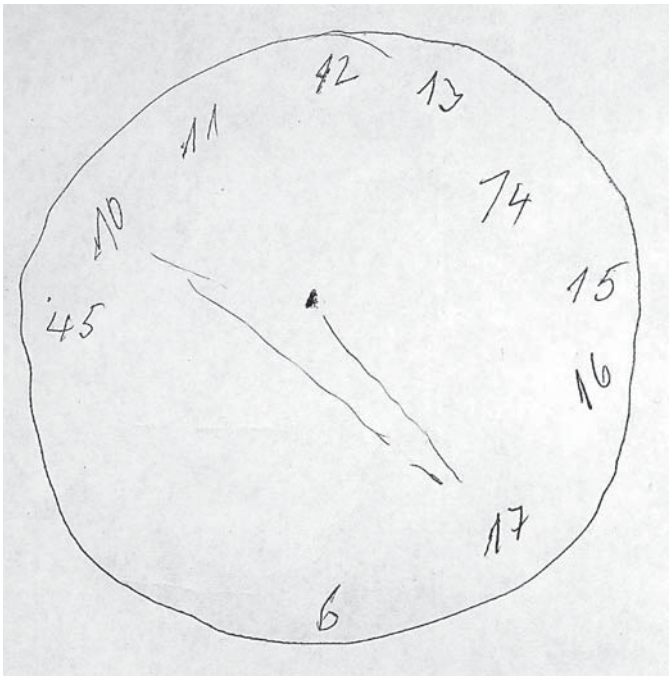


**Fig. 3.** Clock drawing by a 74-year-old patient with PD and mild dementia.

Mechanisms

Nigrostriatal and mesolimbic dopamine deficits have been linked to executive disturbances. Cholinergic deficits in the nucleus basalis of Meynert and cortical neuronal loss are considered essential for PDD. Other transmitter deficits, noncortical (e.g. limbic) changes and concomitant Alzheimer's disease-like pathology probably also play a role [38].

Similar morphological and functional (e.g. brain PET) findings in PDD and DLB, together with overlapping clinical features, suggest that the two disorders actually represent different degrees of a single disorder [39].

Diagnosis

Verbal fluency, Wisconsin card sorting and the Stroop test are useful to assess executive functions. However, there are only few systematic data on screening and assessment scales for cognitive changes in patients with PD [40–43]. The Mini-Mental State Exam has a much lower sensitivity for the diagnosis of PDD than the Montreal Cognitive Assessment and even the clock drawing test alone (fig. 3) [42, 44].

Treatment

Dopaminergic drugs but also atomoxetine have been shown to improve executive functions [45, 46]. Donepezil, rivastigmine and more recently also memantine have been shown to improve PDD and DLB [47–49]. Rivastigmine was recently approved for PDD. Guidelines for the management of PDD have recently been published [50].

## Sleep-Wake Disturbances

### *REM Sleep Behavior Disorder*

Clinical Features

REM sleep behavior disorder (RBD) corresponds to dream enactment behavior during REM sleep. Patients experience vivid, frightening dreams, leading to vocalizations (talking, shouting, screaming, yelling), violent behaviors (kicking, punching, assaults) and injuries.

RBD is estimated to occur in 25–50% of PD patients [51, 52]. This parasomnia of REM sleep can precede the onset of PD by over 10 years [53]. Idiopathic RBD is associated with subtle memory, color discrimination, olfactory and finger tapping deficits which are consistent with an early (preclinical) PD stage [54]. Most patients with idiopathic RBD eventually develop a neurodegenerative disorder (including PD) over the course of time [55, 56].

In patients with PD, RBD is associated with sleep disruption and hallucinations but not with gait impairment/postural instability [57, 58].

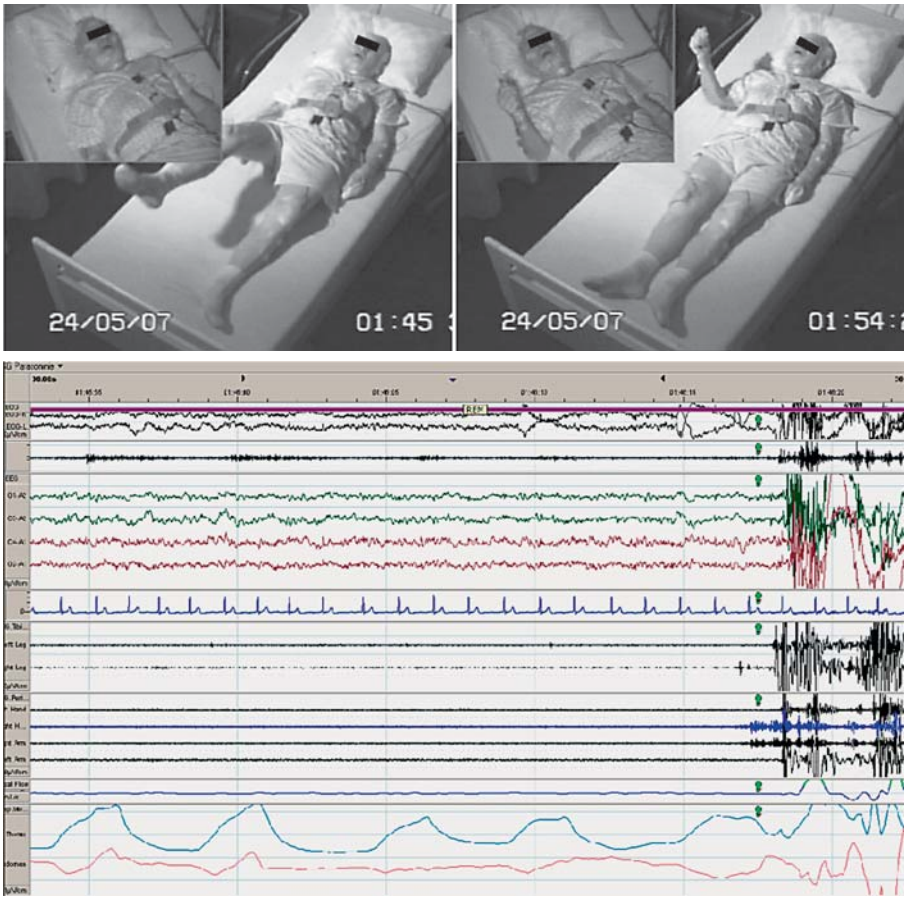


**Fig. 4.** An 82-year-old man with mild parkinsonism and RBD. According to his wife, he displayed frequent vocalizations and violent behavior during sleep. Polysomnographic recordings show loss of normal muscle atonia during REM sleep and increased phasic muscle activity as well as acting out of dreams with kicking and menacing gestures.

Mechanisms

Loss of physiological muscle tone and increase in phasic motor activity during REM sleep are the hallmarks of RBD (fig. 4) [59]. Changes in GABA, dopamine and cholinergic transmission in brainstem (pontomesencephalic) and limbic (amygdaloid) pathways have been postulated [59, 60].

Diagnosis

Recently, a 10-question screening tool was developed and validated for RBD [57, 61]. The sensitivity is high but the specificity is relatively low.

Treatment

Clonazepam (05–2.0 mg at bedtime) but also dopaminergic drugs and melatonin can improve RBD [59]. Mirtazapine, venlafaxine, tricyclic antidepressants and SSRIs have been reported to trigger/worsen RBD in PD [59, 62].

***Sleepwalking***

Clinical Features

Sleepwalking corresponds to a complex sleep-associated behavior, which includes locomotion, mental confusion and amnesia for the episode. Self-inflicted injuries and acts of violence as well as episodes of sleep eating (somnophagia) may also occur [63]. A recent systematic, questionnaire-based survey of 417 patients suggested a 9% frequency of sleepwalking in PD [Oberholzer et al., in preparation]. Half of these patients first developed sleepwalking as adults. Sleepwalking was associated with RBD, nightmares and hallucinations.

Mechanisms

Deficient (ascending) mechanisms of arousal and (descending) mechanisms of motor and muscle tone control have been postulated for both RBD and sleepwalking.

Diagnosis

The differentiation between RBD and sleepwalking may be difficult based on history alone; in addition, the conditions may coexist (see above). The polysomnographic characteristics of PS patients with sleepwalking are essentially unknown.

Treatment

There are no data on treatment of sleepwalking in PD.

***RLS and Periodic Limb Movements in Sleep***

Clinical Features

Typical RLS may precede or (more commonly) follow the onset of PD. It is usually mild. RLS-like sensory symptoms are not unusually reported during wearing-off and off periods but also in dystonic/dyskinetic and (external or internal) tremulous states [64]. Distinguishing between RLS and RLS-like symptoms in patients with fluctuating PD is, in fact, difficult; this may explain the wide range (0–52%) of RLS frequency in PD reported in the literature [65–67].

Most PD patients are not aware of periodic limb movements in sleep (PLMS). The exact frequency of PLMS in PD is poorly known [67]. RLS and PLMS may improve or worsen (maybe because of a dopaminergic withdrawal) after deep brain stimulation.

RLS and PLMS may contribute to insomnia, EDS and daytime fatigue in PD.

Mechanisms

Reduced striatal dopaminergic transmission and low ferritin levels have been postulated to explain RLS and PLMS in PD [67, 68].

Diagnosis

Clinically typical RLS and RLS-like symptoms due to fluctuating PD symptoms or anxiety/depression may be difficult to diagnose. The diagnosis of PLMS requires a nocturnal polysomnography or a leg actigraphy.

Treatment

Extended-release dopamine agonists such as rotigotine and monoamine oxidase B inhibitors such as rasagiline may be particularly beneficial for RLS/PLMS in PD [pers. observation].

***Excessive Daytime Sleepiness***

Clinical Features

EDS is present in 25–50% of PD patients and may lead to sudden sleep episodes ('sleep attacks') [69–71]. It is not uncommon for patients to underestimate the severity of EDS (as estimated by subjective and objective measures). The frequency of sleep attacks in PD ranges from 1 to 27% in the literature [70].

The severity of PD, antiparkinsonian drugs (dopamine agonists), sleep disturbances (including sleep-disordered breathing and RLS/PLMS) and dementia are associated with EDS in PD [37, 72]. Treatment with dopamine agonists has been implicated in the appearance of sleep attacks [69, 73–75]. On rare occasions, severe EDS may appear in young patients early in the course of PD without medication [76]. Sleep deprivation can play a role, particularly in patients with dopamine overuse/dysregulation syndrome.

An overlap exists between EDS, sleep attacks and fluctuations in PD patients with dementia and DLB.

Mechanisms

Several factors in addition to neurodegeneration of neuronal pathways necessary for the maintenance of wakefulness may contribute to EDS (see above). Patients with advanced PD present a 20–30% reduction of hypocretin neurons in the lateral hypothalamus [77]. However, most PD patients, even those with EDS, have normal cerebrospinal fluid hypocretin levels [37, 78–80].

Diagnosis

An Epworth Sleepiness Score of >10 indicates the presence of EDS. A short mean sleep latency (<5 min) is found in 20–30% of PD patients [70]. A correlation between subjective (Epworth Sleepiness Score) and objective EDS (as assessed for example with the Multiple Sleep Latency Test) exists in PD patients [72]. Sleep-onset REM episodes were found to be frequent in some but not all systematic studies [79, 81, 82].

Treatment

Change in medication and treatment of sleep disturbances (including sleep-disordered breathing) may improve EDS in PD. Naps distributed over the day may effectively reduce sleep pressure [pers. observation]. Modafinil has been shown in some but not all studies to improve EDS in PD [83–85].

More recently, sodium oxybate was found to improve EDS and fatigue and an inverse agonist of the histamine $H_3$ receptor to improve EDS in PD [86, 87].

***Fatigue and Apathy***

Clinical Features

Fatigue corresponds to a subjective feeling of exhaustion, lack of energy, physical and mental tiredness (central fatigue) and decreased force generation or rapid fatigability (peripheral fatigue). Apathy is defined as a disorder of motivation with diminished goal-oriented behavior and cognition. Fatigue and apathy are often unrecognized, although systematic studies have shown that they may be present in up to 50% of PD patients [4, 71, 88]. Fatigue can be very disabling in up to 1/3 of patients and appears early in the course of PD [4]. In PD, fatigue is associated with depression, PD severity and sleep disturbances [4, 71]. Apathy has been linked mainly to depression and cognitive decline [88, 89]. Isolated apathy was recently found to represent a risk factor for the subsequent development of dementia [90]. Fatigue – often in association with other psychiatric and somatic symptoms (see above) – can also be observed in the course of withdrawal from dopaminergic drugs, in particular agonists [13]. Finally, deep brain stimulation can also induce apathy [91].

Mechanisms

Fatigue and apathy are thought to arise from the involvement of dopaminergic (e.g. ventral tegmentum-nucleus accumbens) and nondopaminergic (frontosubcortical circuits) mediation of goal-oriented and reward behaviors.

Diagnosis

Apathy, depression and fatigue are sometimes difficult to differentiate because of similar comorbidities and overlapping clinical characteristics. The Fatigue Severity Scale, the Parkinson Fatigue Scale and the Apathy Evaluation Scale have been used as diagnostic tools in PD [71, 91–93].

Treatment

Dopaminergic drugs (e.g. ropinirole) can improve fatigue and apathy, particularly early in the course of PD; methylphenidate can improve central fatigue and levodopa peripheral fatigue [4]. Modafinil improves EDS but not fatigue [94]. Sodium oxybate can improve fatigue and EDS [86].

***Insomnia***

Clinical Features

Sleep induction and maintenance problems are frequent (<50% of PD patients) and may fluctuate over time [95, 96]. Insomnia is more common in female patients with depression and long disease duration [96].

Anxiety/depression, hallucinations, tremor, RLS and the use of activating drugs (e.g. SSRIs) are associated with sleep onset insomnia in PD. On the other hand, PLMS, sleep-disordered breathing, nycturia, nightmares, motor off symptoms/early-morning foot dystonia and motor hyperactivity in sleep/parasomnias are linked to sleep maintenance insomnia in PD.

Mechanisms

Insomnia in PD is often multifactorial. Neurodegeneration per se, PD motor and nonmotor manifestations, drugs and concomitant disorders may cause insomnia.

Diagnosis

Sleep questionnaires, including the Parkinson Disease Sleep Scale [97], as well as wrist actigraphy can be used for screening of sleep disorders/insomnia in PD. Video-polysomnography may be considered in unclear and treatment-unresponsive cases.

Treatment

Extended-release dopamine agonists can improve nocturnal sleep in PD, but the scientific evidence for this effect is poor. Zolpidem, clozapine and sedating antidepressants have also been used for insomnia in PD [98]. Deep brain stimulation was reported to consolidate sleep and improve sleep architecture [99]. Bright light in the morning hours may improve insomnia and daytime sleepiness, but also cognition, depression and even motor functions in advanced/fluctuating PD [100, 101].

***Snoring/Sleep-Disordered Breathing ('Sleep Apnea')/Other Breathing Sounds***

Clinical Features

Snoring and sleep-disordered breathing are more common in PD patients (particularly those with EDS) than controls and may have an impact on sleep and wakefulness. However, only limited data are available on this association [79, 102, 103].

Nocturnal inspiratory stridor (a high-pitched sound which resembles a donkey braying) and expiratory phonation can be observed in PD and other parkinsonian syndromes (e.g. multisystem atrophy).

Mechanisms

Snoring and sleep-disordered breathing are the expression of insufficient patency of the upper airway during sleep (with turbulent air flow), which in turn may be re-

lated to neurodegeneration per se, medications or associated disorders (e.g. obesity). Inspiratory stridor is typical for multisystem atrophy and is due to laryngospasm or dystonia from neurodegeneration or mechanical causes, including excessive respiratory secretions [104, 105].

Diagnosis

Respirography and video-polysomnography are necessary to diagnose sleep-disordered breathing and stridor.

Treatment

Continuous positive airway pressure is the treatment of choice for sleep-disordered breathing and stridor [106]. However, there are almost no data on the effect of continuous positive airway pressure in sleep-disordered breathing in PD. Dopaminergic drugs can improve nocturnal expiratory phonation but worsen inspiratory stridor (dystonia).

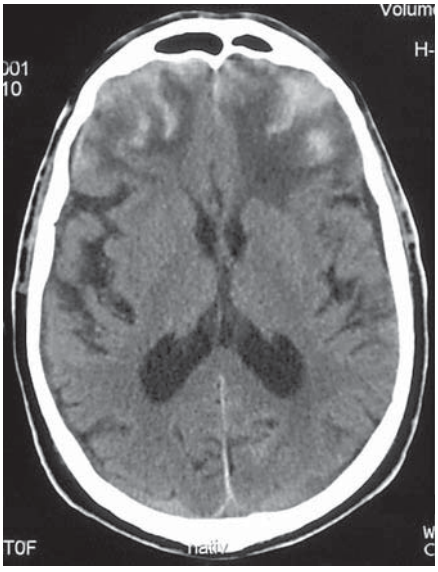


**Fig. 5.** Brain CT of an 83-year-old patient with severe parkinsonism and subdural hematoma following a fall with severe head trauma caused by OH.

## Autonomic Disturbances

### *Orthostatic Hypotension*

Clinical Features

OH (defined as a fall in systolic blood pressure of at least 20 mm Hg) is found in 20–50% of PD patients and is associated with advanced age, male gender and duration and severity of PD [107, 108]. OH is often asymptomatic in PD. Severe and symptomatic OH early in the course of parkinsonism suggests a diagnosis of an atypical Parkinson syndrome [109].

OH, often in association with other psychiatric and somatic symptoms (see above), can be observed in the course of withdrawal or, paradoxically, also potentiation of dopaminergic drugs (fig. 5), in particular agonists [13].

OH is associated with other signs of dysautonomia (e.g. constipation, bladder disturbances, hyperhidrosis, erectile dysfunction) as well as with balance problems and falls [10, 110].

Mechanisms

Vasomotor and cardiac sympathetic dysfunction due to neurodegeneration of autonomic nuclei and pathways is thought to cause OH [108]. Cardiac sympathetic dysfunction can be demonstrated by $^{123}$I-MIBG cardiac scintigraphy [108].

Diagnosis

Orthostatic symptoms are not very sensitive for the presence of OH in PD patients [111]. Blood pressure should be measured on standing for more than 3 min because the appearance of OH may be delayed [111]. The Scale for Outcomes in PD for Autonomic Symptoms (SCOPA-AUT) questionnaire, developed to assess autonomic dysfunction in PD, includes 3 cardiovascular items [112].

Treatment

Nonpharmacological measures (drinking water in the morning before standing, leg crossing, elastic bandage, increased water/salt intake distributed during the day) as well as such drugs as fludrocortisone, domperidone, midodrine and pyridostigmine have been shown to improve OH in PD [113, 114].

### *Bladder Disturbances*

Clinical Features

Urinary disturbances are present in 25–50% of patients with PD [115, 116]. They are more often irritative (nocturia, frequency, urgency, urge incontinence) and typically follow the onset of motor disturbances. Obstructive/voidance symptoms (hesitancy, weak urinary stream) are less common.

Mechanisms

Irritative symptoms are related urodynamically to detrusor hyperreflexia, which is linked to altered dopami-

nergic transmission in PD. Obstructive symptoms may be related to a voluntary contraction of the perineal floor (to prevent incontinence, pseudodyssynergia) and sphincter bradykinesia. Obstructive symptoms can also be secondary to anticholinergics and anatomical obstruction. Subthalamic deep brain stimulation can cause urinary retention [117].

Diagnosis

The SCOPA-AUT questionnaire, developed to assess autonomic dysfunction in PD, includes 6 urinary items [112]. Urodynamic studies and sphincter electromyography are often needed to correctly interpret urinary disturbances in PD [10, 118].

Treatment

Anticholinergics, oxybutynin, tolterodine and botulinum toxin A injections can improve urinary frequency [10, 119, 120]. Levodopa can improve or worsen bladder disturbances. Rotigotine and deep brain stimulation have been shown to have a beneficial effect on bladder function [11].

***Gastrointestinal Disturbances***

Clinical Features

Constipation and delayed gastric emptying are among the most common nonmotor symptoms of PD and can precede the onset of motor disturbances by years [121]. Abnormal salivation and dysphagia are less common. Constipation and nausea can also result from dopaminergic treatment.

Mechanisms

Direct involvement of the gut (including degeneration of the colonic myenteric plexus) but also central (brainstem) mechanisms have been discussed.

Diagnosis

The SCOPA-AUT questionnaire, developed to assess autonomic dysfunction in PD, includes 7 gastrointestinal items [112]. The Swallowing Disturbance Questionnaire and Dysphagia-Specific Quality of Life are currently suggested for the diagnosis/assessment of sialorrhea in PD [122].

Video esophagram, dynamic abdominal scintigraphy (for gastric emptying), colon transit studies, defecography and anorectal manometry have only rarely been systematically assessed in PD patients.

Treatment

Dopaminergic drugs do not improve constipation, which can be treated with dietary adjustments, oral laxatives (such as macrogol/polyethylene glycol), suppositories, botulinum toxin A injections (for outlet obstruction), sacral nerve stimulation and colostomy [3, 120].

***Sexual Dysfunction***

Clinical Features

Sexual dysfunction can be disabling but is usually not assessed and goes unrecognized in PD. Erectile dysfunction (impotence) and loss of libido, as well as hypersexuality, are most commonly observed. The frequency of compulsive sexual behavior in PD patients may be as high as 10% [6].

Mechanisms

Neurobiological as well as psychosocial factors but also medications play a role in sexual dysfunction. A significant percentage of patients who have received deep brain stimulation report sexual disturbances [10]. Patients with the dopamine overuse (dopamine dysregulation) syndrome present hypersexuality and sometimes paraphilia.

Diagnosis

There is only one questionnaire that has been validated for the assessment of impulsive-compulsive disorders (including sexual dysfunction) in PD [17].

Treatment

The effects of dopaminergic drugs on erectile dysfunction and loss of libido in PD are unknown. Sildenafil and other phosphodiesterase type 5 inhibitors can be used for erectile dysfunction [3, 120].

***Sialorrhea (Drooling)***

Clinical Features

Sialorrhea affects about 50% (32–74%) of PD patients [123]. Frequent drooling is reported less commonly and is associated with advanced stages of PD. Sialorrhea is associated with significant psychosocial distress and isolation. Furthermore, it can lead to aspiration pneumonia.

Mechanisms

Impaired or infrequent swallowing, rather than hypersecretion, are considered the cause of sialorrhea.

Diagnosis

The Drooling Severity and Frequency Scale, the Drooling Rating Scale and the Sialorrhea Clinical Scale for PD are currently suggested for the diagnosis/assessment of sialorrhea in PD [122].

Treatment

Anticholinergics, botulinum toxin, surgical interventions, radiotherapy, speech therapy and trials of devices can improve sialorrhea in PD [124]. Recently, 1 mg of oral glycopyrrolate 3 times daily was shown to be superior to placebo for sialorrhea in PD patients (class I evidence) [120, 125].

## Sensory Disturbances

### *Olfaction*

Clinical Features

Decreased olfactory function is present in >70% of patients with PD [126]. Patients usually do not report changes in smell. Specific odors such as those for banana, cinnamon and pineapple may be preferentially affected [127]. Some patients may complain of altered/distorted smell ('smoky odor'). Olfactory dysfunction is typically bilateral and may precede the onset of motor symptoms of PD by years [128]. An association between olfactory dysfunction and idiopathic RBD has been found [129].

An association between anosmia and autonomic failure has recently been recognized [126].

Mechanisms

Nondopaminergic degeneration of the olfactory bulb and the olfactory system has been demonstrated to occur early in the course of PD [130].

Diagnosis

Olfactory acuity, identification, discrimination and memory can be tested with so-called 'Sniffin sticks' and the University of Pennsylvania Smell Identification Test [126, 131].

Treatment

No treatment for smell disturbances is known.

### *Sensory Symptoms/Pain*

Clinical Features

Sensory symptoms, including pain and burning pain in the extremities and trunk, are present in about 50% of patients and may precede the onset of motor symptoms of PD [132–134]. Musculoskeletal pain often involves the body side in which PD motor symptoms first appear. Dystonic pain appears often during wearing-off phases and early morning hours. Pain, often in association with other psychiatric and somatic symptoms (see above), can be observed in the course of withdrawal from dopaminergic drugs, in particular agonists [13]. Neuropathic (e.g. burning) pain may involve oral and genital areas and may be more common in advanced PD [135]. Patients with PD also exhibit a higher frequency of radicular pain/problems than the general population. RLS-like symptoms in PD (see above) may become painful.

An association between pain and depression is known in PD.

Mechanisms

Pain may be related to motor dysfunction/fluctuations and secondary causes (musculoskeletal changes). Central neuropathic mechanisms may also play a role [134].

Diagnosis

Only a few systematic studies, for example using the Brief Pain Inventory, have examined pain in PD [134].

Treatment

A possible underlying cause/component of pain other than PD should be investigated and, if present, treated. Methylphenidate, dopaminergic drugs and deep brain stimulation can directly improve pain due to PD [136, 137].

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